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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61B 5/00

A1

(11) International Publication Number: WO 98/10698

(43) International Publication Date: 19 March 1998 (19.03.98)

(21) International Application Number: PCT/US97/16309

(22) International Filing Date: 15 September 1997 (15.09.97)

(30) Priority Data:
08/713,401 13 September 1996 (13.09.96) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/713,401 (CON)
Filed on 13 September 1996 (13.09.96)

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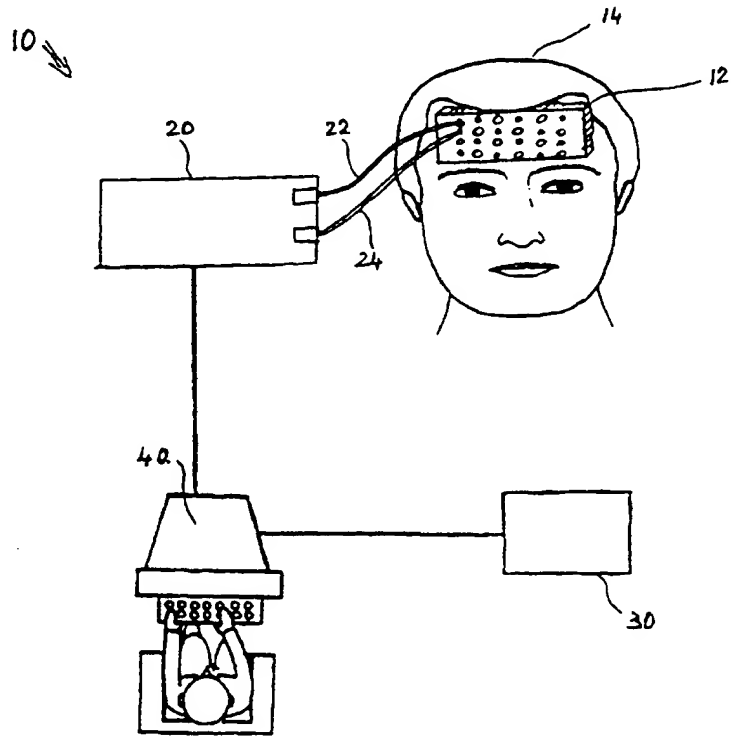
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NON-INVASIVE IMAGING OF BIOLOGICAL TISSUE

(57) Abstract

An optical system (10) for *in vivo*, non-invasive imaging of tissue change includes an optical module (12) with an array of input ports and detection ports located in a selected geometrical pattern to provide a multiplicity of arrayed single source, single detector pairs engaged directly with the subject; a spectrophotometer (20) including a light source constructed to introduce electromagnetic radiation of visible or infrared wavelength into the examined tissue successively at the input ports, the wavelength being sensitive to a constituent of the imaged tissue; a detector constructed to detect, at the detection ports, radiation of the selected wavelength that has migrated in the tissue from respective input ports; and a processor receiving signals of the detected radiation from the detector, and constructed and arranged to create a defined spatial image of the tissue by effectively producing from signals from the multiplicity of arrayed single source, single detector pairs, a succession of data sets representing, from a selected view, a succession of spatial images of the tissue, and an image data set related to differences between data of the successive data sets. Imaging instruments and a method are also described.



NON-INVASIVE IMAGING OF BIOLOGICAL TISSUE

The invention provides proof in principle of the practicality for medical purposes of imaging body tissue, and in particular, neural tissue, especially the brain, using spectrophotometric techniques.

Certain prior work has produced low resolution shadowgrams of the exterior of the cortex, lacking edges or defined contours.

We have shown that by employing an array of ports for a set of single source, single detector pairs, and by implementing the system to acquire a sequence of data sets, distinct difference image data sets can be realized that are useful in diagnosis and treatment, e.g. on a real time basis, with relatively low expense. Blood volume and oxygenation, for instance, can be directly imaged.

We have demonstrated in brain models and human brains, that an optical imaging device can localize the activated area of the human brain. We have produced defined images that show that single functions of the brain such as observing an object (visual), moving a small part of the body (sensory motor) and thinking (cognition) appear to activate only an area as small as 0.5 to 1 cm of the brain cortex. The place of activation observed from the produced image was where it was expected. In the case of side-by-side source and detector pair, between which the probability pattern of photons takes a banana shape, the theoretical resolution and sensitive depth depends on the source-detector distance (half of the distance). By selection of the source-detector distance, a resolution of the image as good as 1.25 cm has been obtained. Imaging of white brain matter to selected depths is realized by increasing the spacing up to 7 cm.

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It is shown that light sources that provide no safety hazard, at relatively low cost can be usefully employed in true imaging. By employing difference measurements, the uncertainties normally limiting continuous wave spectroscopy (CWS) to trend indications are avoided. The greater information content of phase modulation and time resolved spectroscopy leads to even more informative images.

According to one important aspect of the invention, an optical system is provided for *in vivo*, non-invasive imaging of tissue change comprising an optical module including an array of input ports and detection ports located in a selected geometrical pattern to provide a multiplicity of arrayed single source, single detector pairs engaged directly with the subject, a spectrophotometer including a light source means constructed to introduce electromagnetic radiation of visible or infra-red wavelength into the examined tissue successively at the input ports, the wavelength being sensitive to a constituent of the imaged tissue, detector means constructed to detect, at the detection ports, radiation of the selected wavelength that has migrated in the tissue from respective input ports, and a processor receiving signals of the detected radiation from the detector means, and constructed and arranged to create a defined spatial image of the tissue by effectively producing from signals from the multiplicity of arrayed single source, single detector pairs, a succession of data sets representing, from a selected view, a succession of spatial images of the tissue, and an image data set related to differences between data of the successive data sets.

In another important aspect of the invention, an optical system is provided for *in vivo*, non-invasive functional neuroimaging of tissue comprising a

distance being selected according to the tissue depth desired to be imaged.

The optical module or an associated set of the modules is constructed to take readings at different depths to produce 3D data sets from which an image date set may be produced.

The processor is adapted to produce the image data set by implementing an optical tomography algorithm.

The optical tomography algorithm preferably employs factors related to determined probability distribution of photons attributable to the scattering character of the tissue being imaged.

The optical system is constructed to form the image data set from a part of the head. In particular embodiments the optical system is constructed to form the functional image data set from below the surface region of the cortex.

The stimulator is constructed to stimulate the visual cortex, the cognitive cortex, the sensory motor cortex, or spinal tissue.

In various embodiments the stimulator is constructed to deliver electrical signals to selected tissue, apply an electrical field to selected tissue, or deliver magnetic signals to selected tissue.

In various embodiments the image set is related to at least one of the group consisting of blood volume, hemoglobin oxygenation or deoxygenation, photon absorption coefficient, photon scattering coefficient, refractive index, change in magnetic field, change in electric field, production of or change of a specific tissue constituent, and production of or change in the concentration of a pigment.

In various embodiments the tissue constituent is an endogenous pigment, for example hemoglobin, or an exogenous pigment, for example a selected contrast agent.

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In certain other embodiments the spectrophotometer includes a light source means that is constructed to generate pulses of radiation of the wavelength, the pulses having duration on the order of a nanosecond or less, the detector means being constructed to detect over time photons of modified pulses that have migrated in the tissue from the input ports, an analyzer, connected to the detector means, adapted to determine a change in the pulse waveform shape of the detected pulses relative to the introduced pulses, at the wavelength, and the processor being constructed and arranged to create the image data set based on the determined pulse waveform change.

Preferably, this processor is constructed and arranged to calculate the effective pathlength of photons of the wavelength migrating between the input and detection ports in conjunction with creating the image data set.

In certain embodiments of this aspect of the invention the processor is constructed and arranged to calculate the scattering coefficient at the wavelength in conjunction with creating the image data set.

Also, in certain embodiments, the processor is constructed and arranged to calculate the absorption coefficient at said wavelength in conjunction with creating the image data set.

In preferred embodiments the optical system is constructed to introduce and detect photons at two wavelengths selected to provide sensitivity to a property of the constituent.

In certain preferred embodiments, the source means of the optical system comprises an incandescent lamp, and preferably a set of miniature lamps directly contacting the subject.

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source at a time enabling accumulation of single source-detector responses.

The light source or sources are incandescent lamps, LEDs, laser diodes or other lasers.

The instrument comprises an array of sources of near infrared or visible photons, an array of detectors positioned to receive photons from the sources in respective source-detector pairs following migration of the photons from the sources through the tissue, a system enabling numerous readings of migrated photons to be taken systematically at the detectors for different source-detector positions relative to the tissue, and a processor employing an imaging algorithm based on respectively different probabilities for a given source-detector position, for photons from the source passing through different regions of the volume of the scattering tissue that are located at different positions distributed laterally from a straight reference line between source and detector.

According to another important aspect of the invention, an instrument is provided for functional imaging of brain activity of a subject comprising an imager constructed and arranged to image hemoglobin, deoxyhemoglobin or blood volume, the imager comprising an array of sources of near infrared or visible photons, and array of detectors positioned to receive photons from the sources following migration of photons from the sources through the tissue, a system enabling numerous readings of migrated photons to be taken systematically for different source-detector positions relative to the tissue, and a processor employing data sets taken during rest and during stimulation, with an imaging algorithm that is based on respectively different probabilities for a given source-detector position, for photons from the source passing through different regions of the volume of

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subject an imaging instrument according to any of the foregoing aspects. In certain preferred embodiments of the methods an optical contrast agent or a drug is introduced to the blood stream of the subject, and the instrument is employed to produce an image data set for the tissue while the contrast agent or drug is present in blood circulating in the tissue of the subject or is present in localized tissue.

These and other features and advantages of the invention will be understood from the drawings, the following description of preferred embodiments and the claims.

Brief Description of the Drawings

Fig. 1 depicts a block diagram of an optical tomography system for imaging functional activity of the brain.

Fig. 2 depicts a diagram of an optical module employed in one preferred embodiment of the system of Fig. 1.

Fig. 2A depicts a schematic circuit diagram of a continuous wave spectrophotometer employed in one preferred embodiment of the system of Fig. 1.

Figs. 3A and 3B depict differential images of blood volumes detected on the visual cortex of a man watching a monitor screen and after a rest period of 2 minutes, respectively.

Figs. 4A, 4B and 4C depict differential images of blood volumes of the motor cortex of a man tapping his fingers, after a rest period of 30 seconds, and restored rest volumes at 30 - 60 seconds, respectively.

Figs. 5A, 5B and 5C depict differential images of the hemoglobin oxygenation of the prefrontal cortex of a man translating words from English to French.

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component, that absorbs superficial photons not propagating in the examined tissue.

Spectrophotometer unit 20 is a continuous wave spectrophotometer, as described in the WO 92/20273 publication published November 26, 1996, now pending as U.S. patent application serial no. 08/150,084, which is incorporated by reference as if fully set forth herein. Alternatively, spectrophotometer unit 20 is a time resolved spectrophotometer, as described in the U.S. Patents 5,119,815 and 5,386,827, or a phase modulation spectrophotometer, as described in the U.S. Patents 4,972,331 and 5,187,672, and in the co-pending U.S. patent application 08/031,945 all of which are incorporated by reference as if fully set forth herein.

Stimulation unit 30 is constructed to stimulate a specific neural function of a subject. The stimulator, controlled by computer 40, emits mechanical, electrical, thermal, sound or light signals designed to stimulate the neural activity of interest. The neural activity is induced by sensory stimuli, such as visual, auditory, or olfactory stimuli, taste, tactile discrimination, pain and temperature stimuli, or proprioceptive stimuli.

In a first preferred embodiment, a continuous wave spectrophotometer includes several sources and detectors attached to the optical module mounted on the head of the examined subject. Referring to Fig. 2, optical module 12a includes twelve light sources S1, S2, ..., S12 and four light detectors D1, D2, D3, and D4 mounted on a plastic material. The light sources and the light detectors are located on a geometrical pattern that provides sixteen source-detector combinations (C1, C2, ..., C16) having a selected source-detector separation. The separation was selected to be 2.5 cm, which produces about 1.25 cm average light penetration, to obtain a two dimensional image of the cortical surface. The light

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charging current in the first step. This is achieved using an appropriate ON/OFF combination of switches A and B. The voltage of capacitor 58 is charging to a value which, after 200 msec., represents the total detected intensity minus the dark level noise signal. In the third step, both switches A and B are turned OFF to disconnect both the positive unity gain and the negative unity gain operational amplifiers (60 and 62). Then, the output of integrator 58 is moved via switch C to an analog-to-digital converter and the digital signal is stored in the memory of computer 60. In the fourth step, the switches A, B and C are open and switch D is closed in order to discharge capacitor 58 through a 47K resistor. At this point, the circuit of integrator 56 is reset to zero and ready for the first step of the detection cycle.

Alternatively, analog circuit 50 may be replaced by a computer with an analog-to-digital converter and appropriate software that controls the entire operation of optical module 12A. For instance a source code and be written in C language, to control the sources and the detectors of optical module 12A in a similar way as described above. The detected dark level noise signal is digitally subtracted from the detected intensity of the introduced light. A program can also be readliy written to transfers the raw data file, written in C, to another format for further use by the imaging algorithm.

This optical tomography system was used to image the activity of the visual cortex of a 54 year-old male subject while strictly observing the established safety protocol. Optical module 12A was placed on the occipital bone of the skull to observe the surface of the occipital cortex. A first data set was acquired for all sixteen C1 through C16 combinations with the subject having his eyes closed. A second data set was collected while the

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of the parietal cortex. Similarly as above, a first data set was acquired for all sixteen C1 through C16 combinations with the subject having his fingers in rest. A second data set was collected while the subject was tapping as fast as possible for about 40 seconds, and a third data set was acquired after a rest period of 30 seconds. A fourth data set was acquired after a rest period of 30-60 seconds. Figs. 4A, 4B and 4C depict differential images of blood volumes of the motor cortex of the subject man tapping his fingers, after a rest period of 30 seconds, and restored rest volumes at 30 - 60 seconds, respectively. The images show an increased blood volume, which is accompanied with desaturation of hemoglobin in the imaged area.

In another experiment, the optical tomography system was used to image the cognitive activity in the prefrontal cortex of a subject. A high school student was asked to translate words from English to French for 40 seconds with resting periods of 2 minutes. Figs. 5A, 5B and 5C depict differential images of the hemoglobin oxygenation of the prefrontal cortex of a man translating words from English to French during three successive periods of 40 seconds. In an area of 0.5 x 2 cm of the prefrontal cortex, the images show repeated increased blood oxygenation due to the activation in a specific part of the cortex. However, the first image of the first stimulus produced the highest oxygenation increase. Similarly, Figs. 6A, 6B and 6C depict differential images of the blood volumes in the same area of the prefrontal cortex during the translation from English to French.

In another important embodiment, a three dimensional image is created by producing slices of the above described two dimensional image at different depths of average photon penetration. The optical module includes a hairbrush optical coupler disclosed in the PCT

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The optical module is constructed to maintain a selected separation of the input and detection ports. In a reflection geometry, the photons of the introduced light migrate over a "banana" pattern with an average penetration depth about one half on the input-detection port separation. Thus, a neural region is targeted by the location and separation of the ports of optical module 12. The exterior locations of the ports depend on the targeted neural region. The locations of the neural regions have been extensively mapped in the prior art and are known to a person skilled in neuroanatonomy and neurophysiology.

The computer uses a backprojection algorithm known in computed tomography (CT) modified for light diffusion and refraction and the banana like geometry employed by the optical imaging system. In the optical backprojection algorithm, the probabilistic concept of the "photon migration density" replaces the linear relationship of ballistically transmitted X-rays, for the beam representing pixels. The photon migration density denotes a probability that a photon introduced at the input port will occupy a specific pixel and reach the detection port. For different types of tissue, the phase modulation spectrophotometer provides the values of the scattering and absorption coefficients employed in the probability calculations. In the image reconstruction program, the probability is translated into a weight factor, when it is used to process backprojection. The backprojection averages out the values of information that each beam carries with the weighting in each pixel. The specific algorithms are embodied in the source code provided in Appendices E and F. Appendix E is a source code that incorporates a weighting algorithm for creating a photon density image used in the backprojection reconstruction algorithm disclosed in Appendix F.

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oculocephalic reflexes, oculovestibular reflexes, deep tendon reflexes, abdominal reflex, cremasteric reflexes, postural reflexes, gag reflex, infantile reflexes (such as blinking reflex, cochleopalpebral reflex, palmar grasp reflex, digital response reflex, rooting reflex, Galant's reflex, tonic neck reflex, Perez reflex, startle reflex).

The stimulator stimulates a selected region of the nervous system. The corresponding neurologic impulses, transmitted by the neurons, are detected and imaged at different points of their paths, for example, in the nerves, in the spinal cord, in the thalamus, or in the cerebral cortex. For example, when the stimulator causes a cold or hot stimulation on the little finger of the left hand, this thermal stimulation produces impulses that travel in the right lateral spinothalamic tract of the cervical spinal cord, to the thalamic sensory nuclei and end in the right postcentral gyrus of the parietal lobe.

What is claimed is:

2. An optical system for *in vivo*, non-invasive functional neuroimaging of tissue comprising:

a stimulator constructed to stimulate a selected functional activity of neural tissue of interest;

an optical module including an array of input ports and detection ports located in a selected geometrical pattern to provide a multiplicity of arrayed single source, single detector pairs engaged directly with the subject;

a spectrophotometer including

light source means constructed to introduce electromagnetic radiation of visible or infra-red wavelength into the examined neural tissue successively at the input ports, the wavelength being sensitive to a tissue constituent associated with a physiological response of the imaged functional activity;

detector means constructed to detect, at said detection ports, radiation of the selected wavelength that has migrated in the stimulated neural tissue from respective input ports; and

a processor receiving signals of said detected radiation from said detector means, and constructed and arranged to create a defined spatial image of the functional activity of neural tissue by effectively producing from the signals from the multiplicity of arrayed single source, single detector pairs, a first data set representing, from a selected view, a spatial image of the neural tissue at rest, a second data set representing, from the same selected view, a spatial image of the neural tissue during stimulation, and a functional image data set that is related to the differences between said first and second data sets, over said sets.

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10. The optical system of claim 2 wherein said stimulator is constructed to stimulate the cognitive cortex.

11. The optical system of claim 2 wherein said stimulator is constructed to stimulate the sensory motor cortex.

12. The optical system of claim 2 wherein said stimulator is constructed to stimulate spinal tissue.

13. The optical system of claim 2 wherein said stimulator is constructed to deliver electrical signals to selected tissue.

14. The optical system of claim 2 wherein said stimulator is constructed to apply an electrical field to selected tissue.

15. The optical system of claim 2 wherein said stimulator is constructed to deliver magnetic signals to selected tissue.

16. The optical system of claim 1 or 2 wherein said image set is related to at least one of the group consisting of blood volume, hemoglobin oxygenation or deoxygenation, photon absorption coefficient, photon scattering coefficient, refractive index, change in magnetic field, change in electric field, production of or change of a specific tissue constituent, and production of or change in the concentration of a pigment.

17. The optical system of claim 1 or 2 wherein said tissue constituent is an endogenous pigment.

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23. The optical system of claim 22 further comprising

a second oscillator constructed to generate a second waveform at a second frequency;

said detector means arranged to receive a reference waveform at a reference frequency offset by a frequency on the order of 10^3Hz from said first frequency and to produce a signal, at said offset frequency, corresponding to said detected radiation; and

said phase detector adapted to compare, at said offset frequency, the detected radiation with the introduced radiation and to determine therefrom the phase shift at said wavelength.

24. The optical system of claim 1 wherein said spectrophotometer includes

a light source, means constructed to generate pulses of radiation of said wavelength, said pulses having duration on the order of a nanosecond or less;

said detector means being constructed to detect over time photons of modified pulses that have migrated in the tissue from said input ports;

an analyzer, connected to said detector means, adapted to determine a change in the pulse waveform shape of said detected pulses relative to said introduced pulses, at said wavelength; and

said processor being constructed and arranged to create said image data set based on said determined pulse waveform change.

25. The optical system of claim 24 wherein said processor is constructed and arranged to calculate the effective pathlength of photons of said wavelength migrating between said input and detection ports in conjunction with creating said image data set.

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31. An instrument for functional imaging of brain activity of a subject comprising a brain imager, including an array of sources and detectors defining a multiplicity of source-detector pairs, constructed and arranged to image hemoglobin, deoxyhemoglobin or blood volume at depth within the brain during administration of a respective stimulus to the subject, said brain imager including

a processor receiving signals of said detected radiation from said detector, and constructed and arranged to create a defined spatial image of the functional activity of neural tissue by effectively producing a first data set representing, from a selected view, a spatial image of blood in the cortex while the subject is at rest, a second data set representing, from the same selected view, a spatial image of the blood in the cortex during stimulation, and a functional image data set that is related to the differences between said first and second data sets, over said sets.

32. The device of claim 31 in the form of a near infrared hemoglobinometer based on introducing and detecting photons that have migrated through tissue of the head.

33. The device of claim 32 having multiple source-detector pairs for engaging the skull, the source being spaced from the detector for selected pairs between about 1.5 and 7 cm.

34. The device of claim 33 in which the spacing is 2.5 cm or greater.

38. An instrument for functional imaging of brain activity of a subject comprising an imager constructed and arranged to image hemoglobin, deoxyhemoglobin or blood volume, said imager comprising

an array of sources of near infrared or visible photons,

an array of detectors positioned to receive photons from the sources following migration of photons from the sources through the tissue,

a system enabling numerous readings of migrated photons to be taken systematically for different source-detector positions relative to the tissue, and

a processor employing data sets taken during rest and during stimulation, with an imaging algorithm that is based on respectively different probabilities for a given source-detector position, for photons from the source passing through different regions of the volume of the scattering tissue that are located at different positions distributed laterally from a straight reference line between source and detector.

39. The imaging instrument of claim 37 or 38 in which the imaging algorithm is a back-projection algorithm, and said probabilities are implemented as respectively different weight factors employed in the algorithm for detected energy for different pixels of the image.

40. The instrument of claim 31, 37 or 38 constructed to store at least one set of data for a given area of the brain while the subject is at rest and at least one set of data for the given area of the brain while the subject is stimulated, and to produce a defined output image representing the differences over the area of the respective sets of data.

47. The method of claim 46 including introducing an optical contrast agent or a drug to the blood stream of the subject, and

producing with the instrument an image data set for the tissue while the contrast agent or drug is present in blood circulating in the tissue of the subject or is present in the localized tissue.

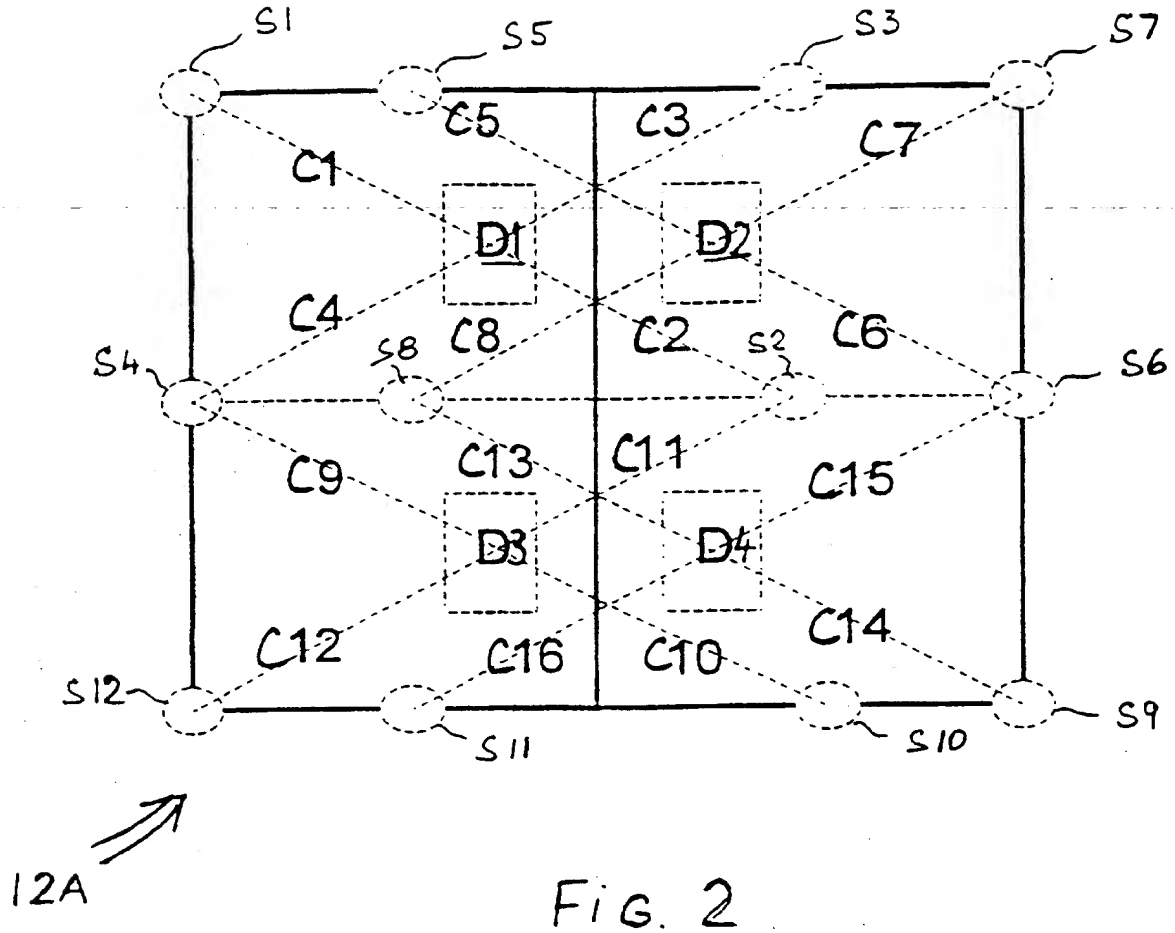

FIG. 2

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FIG. 3A

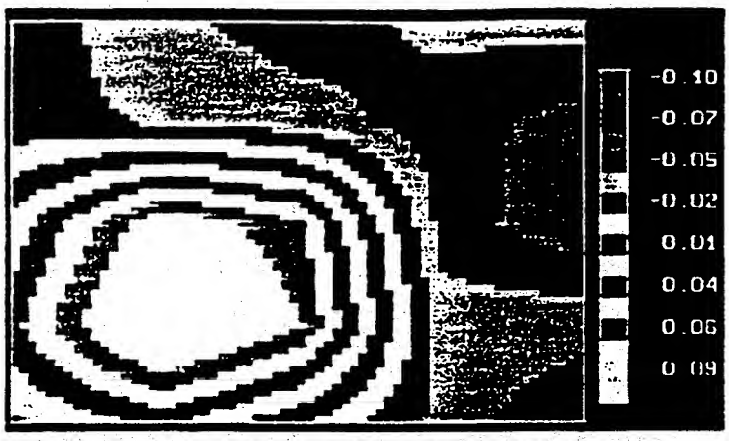
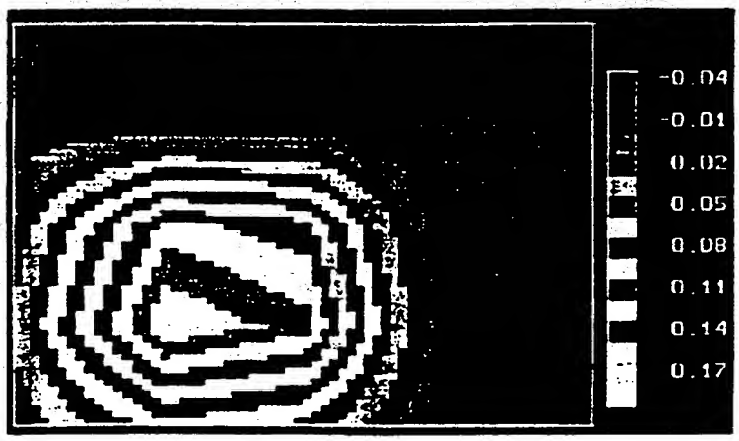


FIG. 3B



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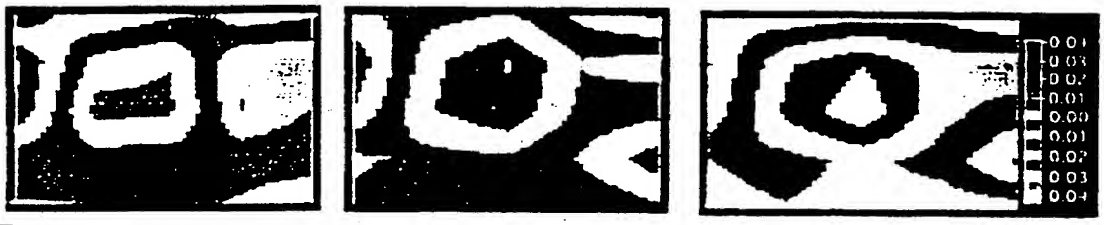
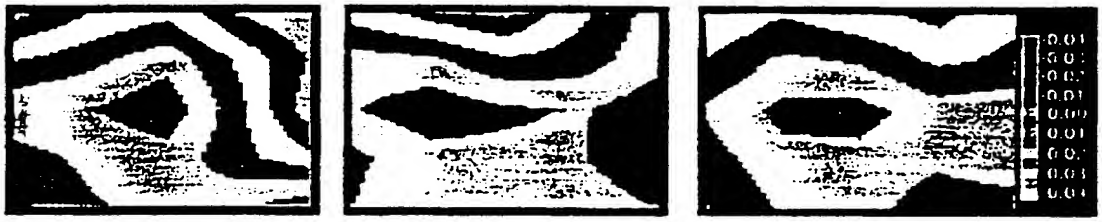
FIGS. 5A 5B 5C



FIGS. 6A 6B 6C



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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/16309

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61B5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
29 January 1998	10/02/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chen, A

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 88 01485 A (SINGER) 10 March 1988 see abstract see page 11, line 7 - page 13, line 20	5,24,30, 37,39,41
A	US 4 940 453 A (CADWELL) 10 July 1990 see column 7, line 11 - column 8, line 54 see figures 2-4	11,13-15
A	US 5 143 081 A (YOUNG ET AL.) 1 September 1992 see column 17, line 4 - line 45	12

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